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REVIEW ARTICLE

Lifestyle use of drugs by healthy people for enhancing cognition, creativity, motivation and pleasure

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Today, there is continued, and in some cases growing, availability of not only psychoactive substances, including treatments for mental health disorders such as cognitive enhancers, which can enhance or restore brain function, but also 'recreational' drugs such as novel psychoactive substances (NPS). The use of psychoactive drugs has both benefits and risks: whilst new drugs to treat cognitive symptoms in neuropsychiatric or neurodegenerative disorders could have great benefits for many patient groups, the increasing ease of accessibility to recreational NPS and the increasing lifestyle use of cognitive enhancers by healthy people means that the effective management of psychoactive substances will be an issue of increasing importance. Clearly, the potential benefits of cognitive enhancers are large and increasingly relevant, particularly as the population ages, and for this reason, we should continue to devote resources to the development of cognitive enhancers as treatments for neurodegenerative diseases and psychiatric disorders, including Alzheimer's disease, attention deficit hyperactivity disorder and schizophrenia. However, the increasing use of cognitive enhancers by healthy individuals raises safety, ethical and regulatory concerns, which should not be ignored. Similarly, understanding the short- and long-term consequences of the use of NPS, as well as better understanding the motivations and profiles of users could promote more effective prevention and harm reduction measures.

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Abbreviations

ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; EMA, European Medicines Agency; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; FDA, Food and Drug Administration; GABA, gamma-Aminobutyric acid; GABA, gamma-Aminobutyric acid; LSD, Lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; NMDA, N-Methyl-D-aspartate; NPS, novel psychoactive substances; THC, Tetrahydrocannabinol; UNODC, United Nations Office on Drugs and Crime

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Introduction

The use of psychoactive drugs has been a feature of human society for much of recorded history. An emerging trend in recent years has been the increasing use of pharmaceuticals by healthy individuals to enhance cognition, which has attracted both positive (Davies, 2015; Wenner Moyer, 2016) and negative (Serrano, 2015; Zand, 2016) media attention (Partridge *et al.*, 2011). For instance, the Care Quality Commission reported that, consistent with previous years, **methylphenidate** prescribing in the UK increased during 2015, with an 8.7% rise in prescriptions compared with 2014. They attributed this increase to the increased diagnosis of attention deficit hyperactivity disorder (ADHD) by GPs, but importantly, also, to its potential for diversion and misuse (Care Quality Commission, 2016). Similarly, a 2016 survey of 2000 UK students by The Student Room revealed that 1 in 10 had used drugs such as **modafinil** or the peptide nootropic Noopept to study, and a quarter of the sample surveyed said they would consider taking them in the future (The Student Room, 2016). Whilst cognitive-enhancing drugs are needed to treat cognitive symptoms in those suffering from psychiatric and neurodegenerative disorders (Sahakian *et al.*, 2015; Savulich *et al.*, 2017), their use by normal, healthy individuals raises ethical and safety concerns. In particular, the safety and efficacy of these drugs in healthy individuals in the long-term are still unclear.

The use of psychoactive substances by healthy individuals is not limited to enhancing cognition. In parallel to the rise in the use of 'smart drugs', in recent years there has been an unprecedented increase in the emergence and use of formerly called 'legal highs' or novel psychoactive substances (NPS). In 2015 alone, 100 NPS were reported to the EU Early Warning System, bringing the total number of monitored NPS to over 560 (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2016: Trends and developments, 2016) and between 2008 and 2015, a total of 644 NPS had been reported by 102 countries and territories to the United Nations Office on Drugs and Crime (UNODC) early warning advisory on NPS (UNODC, World Drug Report, 2016). NPS are designed to mimic the effects of 'classic' drugs such as cannabis, **cocaine**, **heroin**, **LSD**, **MDMA** ('ecstasy') or **methamphetamine**, but being synthetic derivatives or analogues of these substances means that they often evade relevant drug legislation. Up until very recently, they were sold openly in specialized 'head shops' as well as *via* the Internet, where they are typically marketed as 'bath salt', 'plant food', 'research chemicals' 'club drugs' 'designer drugs' or 'not for human consumption'. The speed at which NPS appear and the relative ease with which they can be obtained on the Internet has strongly contributed to their widespread use (EMCDDA, New psychoactive substances in Europe, 2015a). Indeed, marketed in many different ways and forms, NPS can be observed among several different user groups, including school students, partygoers, 'psychonauts', prisoners and injecting drug users, whose motivations for their use varies from enhancing perception and creativity to pleasure and enjoyment (UNODC, World Drug Report, 2016). Worryingly, evidence indicates that NPS are increasingly linked to hospital emergencies and some drug-induced deaths, mirroring the increasing availability of these substances (EMCDDA, 2015a,b). A recent analysis of hospital emergency data by the European Drug Emergencies Network found that 9% of all drug-related emergencies involved new psychoactive substances, primarily cathinones (EMCDDA, 2015a). However, estimating the risks associated with specific NPS is difficult as people who use drugs often tend to be polydrug users, and NPS seem to be reported increasingly in polydrug use patterns in different regions (UNODC, World Drug Report, 2016). Polydrug use thus potentially exposes the user to additional serious health risks. There have been steps to control this rising trend, with several countries recently implementing legal responses to prohibit the production, distribution and sale of NPS (UNODC, World Drug Report, 2016). Currently, not all NPS are under international control (Miliano *et al.*, 2016), but in the UK, all NPS are now illegal to supply under the Psychoactive Substances Act introduced in May 2016 (Psychoactive Substances Act, 2016). The Act does not include possession as an offence in order to avoid the criminalisation of young people. However, the criminalisation of importation under the Act still threatens to criminalize many young people who buy from offshore online retailers who will inevitably fill the gap as 'head shops' close.

The aim of this review is to summarize studies into the effects of cognitive-enhancing drugs and NPS in healthy individuals. The review also presents research studies exploring the characteristics and motivations of users of these psychoactive substances. Finally, we consider ethical and societal implications of the increasing lifestyle use of cognitive-enhancing drugs and risks associated with NPS use.

Pharmacological cognitive enhancement in healthy people

Drugs with cognitive enhancement potential

Popular prescription drugs used for enhancement purposes are the traditional stimulants primarily used to treat ADHD, including methylphenidate (Ritalin) and **amphetamine**, most widely prescribed as mixed amphetamine salts consisting primarily of dextroamphetamine (Adderall), and modafinil, a relatively novel stimulant primarily used to treat sleep disorders such as narcolepsy, sleep apnoea and shift-work sleep disorder (Sahakian and Morein-Zamir, 2007). Methylphenidate and Adderall are thought to exert their cognitive-enhancing effects primarily by increasing levels of **dopamine** and **noradrenaline** in the prefrontal cortex and the cortical and subcortical regions projecting to it, and this mechanism is responsible for improving attention in ADHD (Wilens, 2006; del Campo *et al.*, 2013). In addition to its primary effects on dopamine and noradrenaline, modafinil also modulates **GABA**, **glutamate**, **5-HT** (serotonin), **histamine** and **orexin** (Minzenberg and Carter, 2007). It is thought that the cognitive-enhancing and task-related motivational effects of modafinil include actions on glutamate, noradrenaline and dopamine (Müller *et al.*, 2004; Scoriels *et al.*, 2013; Porsdam Mann and Sahakian, 2015). Other drugs with purported cognition enhancing effects include **acetylcholinesterase** inhibitors such as **donepezil**, which are used to treat Alzheimer's disease

(Repantis *et al.*, 2010a), β-blockers such as **propranolol** (Maher, 2008; Schelle *et al.*, 2015) and **atomoxetine**, a highly selective noradrenaline reuptake inhibitor also used to treat ADHD (Graf *et al.*, 2011). Given the interaction between motivation, mood and cognitive performance, people are also using drugs that improve sleep, reduce anxiety (e.g. benzodiazepines) and improve mood (e.g. selective 5-HT reuptake inhibitors) (Kordt, 2015).

Prevalence and motivations for enhancement

There have been extensive reports on the use of cognitive-enhancing drugs by students to aid memory and concentration. Amongst university students in Canada and the US, the practice appears to be commonplace and increasing, with recent surveys indicating a prevalence of 11–25% (Singh *et al.*, 2014; Nicholson *et al.*, 2015), an increase from a 2011 review that reported a prevalence in the range of 2–16% (Smith and Farah, 2011). In Europe, use amongst university students appears to be similarly widespread, with surveys in several different countries reporting a prevalence of 1–20% (Nicholson *et al.*, 2015). However, estimates of prevalence vary widely due to differences in substances studied, definitions of non-medical use, methods of sampling and the length of time for which prevalence was reported (lifetime/past year/past month). Moreover, so far, studies suggest that most students use drugs for cognitive-enhancing purposes infrequently, and often during specific periods of high-pressure such as during exam time. Thus, Teter *et al.* (2006) reported mostly sporadic use amongst US students and a study of Swiss university students by Maier *et al.* (2013) found that approximately 70% were using cognitive-enhancing drugs for exam preparation.

Recent emerging evidence suggests that healthy adults are also using cognitive-enhancing drugs to increase productivity in the workplace. A 2015 survey of 5000 workers, issued by a large German health insurance company, found 6.7% using drugs to enhance their performance or cope with anxiety, up from 4.7% in 2009 (Kordt, 2015). There have also been reports in the media of alleged widespread use of cognitive-enhancing drugs in highly competitive industries such as the financial industry (Dunn, 2016) and in the Silicon Valley (Corbyn, 2015). With regard to the latter, an increasingly popular phenomenon reported in the media is ‘microdosing’ – taking sub-perceptual doses of psychedelic drugs such as LSD, psilocybin or mescaline every few days to enhance cognitive function, perception and creativity. Anecdotal evidence suggests that, under pressure to perform, professionals are microdosing psychedelics to enhance performance at work, gain a competitive advantage, stay focused and manage stress. Some find that microdosing psychedelics alongside certain prescribed medications, such as stimulants for ADHD, has allowed them to reduce the dose and associated unpleasant side effects of their prescribed medications. Other people report general positive health effects, such as managing anxiety, sleeping better, eating more healthily and exercising more (Solon, 2016). However, without any laboratory tests into the effects of microdosing as of yet, the evidence is purely anecdotal and the effects – short- and long-term – remain unknown.

These numbers raise the question as to why healthy people are using cognitive-enhancing drugs. Current evidence indicates that some of the main reasons include achieving a competitive advantage at school, university or work and coping with the pressure to succeed; maintaining levels of attention and performance when sleep deprived or jet-lagged; and improving task-related motivation (e.g. for tasks that are difficult to get started or unappealing) (Sahakian and LaBuzetta, 2013; Sahakian *et al.*, 2015; Brühl and Sahakian, 2016). In addition to improving academic results, some students also reported taking cognitive enhancers to maintain an adequate work-life balance (Hildt *et al.*, 2014). In the workplace, the data available indicate that healthy adults use cognitive enhancing drugs to face the ever-increasing stress and demands of the work environment (Brühl and Sahakian, 2016). The German survey found that people particularly prone to using cognitive enhancers were those worried about their jobs, working at the limit of their capabilities, required not to show emotions or working in high-pressure fields where small mistakes can have serious consequences (Kordt, 2015). Users reported the following motives for use: enhancement in specific situations (e.g. examinations, giving a presentation and important negotiations; reported by 41%), work becomes easier (reported by 35%), attainment of goals more easily (32%), more energy and better mood for other interests (27%), competitive edge at work (12%), inability to do the work otherwise (25%), and requirements for sleep become less (9%) (Kordt, 2015).

Effects of cognitive-enhancing drugs in healthy people

In support of their popularity, evidence from several meta-analyses validates the use of ‘smart drugs’ such as modafinil to enhance cognitive performance in healthy, non-sleep deprived individuals (Repantis *et al.*, 2010b; Battleday and Brem, 2015). Although, it may be that expectations regarding the effectiveness of these drugs exceed their actual effects (Repantis *et al.*, 2010b). In the case of stimulants, some studies suggest that it may be the non-cognitive effects of stimulants that are most able to enhance work performance, with subjective effects on energy, confidence and motivation being noted by students as the most helpful effects of amphetamine (Ilieva and Farah, 2013; Vrecko, 2013).

Nonetheless, the use of ‘smart drugs’ by healthy individuals has prompted questions as to which cognitive-enhancing drugs are genuinely effective and for which cognitive domains.

Effects of amphetamine, methylphenidate and modafinil. In a 2010 meta-analysis, methylphenidate was reported to have a positive effect on memory in healthy individuals, with the most prominent positive effect being on spatial working memory, but there was no consistent evidence for any effects on attention and other executive functions (Repantis *et al.*, 2010b). A review by Smith and Farah (2011) found both significant and null effects of stimulants on working memory. They also found an enhancing effect of stimulants on learning under some circumstances, specifically when the retention interval between study and test was longer than an hour, but not for shorter intervals (Smith and Farah, 2011). A 2016 meta-analysis found prescription stimulants improved processing speed accuracy but had no effects on other areas of cognition, including planning, decision-making and cognitive perseveration (Marraccini *et al.*, 2016). Stimulant drugs such as methylphenidate are known to have an inverted U-shaped function, where low baseline performance is enhanced but optimal, high-level performance may not change or may even be reduced (Sahakian and Robbins, 1977; Robbins and Sahakian, 1979). For example, del Campo *et al.* (2013) found that poor sustained attention improved following methylphenidate, whether participants were healthy volunteers or patients with ADHD. Clatworthy *et al.* (2009) found direct evidence for this: methylphenidate in young healthy subjects resulted in distinct changes in **D_2/D_3** receptor availability in different regions of the striatum and the change in receptor availability within an individual subregion predicted cognitive performance on reversal learning and spatial working memory tasks. However, in comparison to studies on typical stimulants, modafinil did not appear to induce any substantial baseline-dependent effects. Baseline levels of performance may lead to differential effects of stimulants on cognition.

Evidence to date indicates that modafinil provokes cognitive enhancing effects in healthy people. A 2010 meta-analysis found that, in well-rested healthy individuals, modafinil moderately improved attention but had no effect on memory, mood or motivation (Repantis *et al.*, 2010b). In moderately sleep deprived individuals, modafinil had a positive effect on wakefulness, executive functions and memory, but no effects on mood (Repantis *et al.*, 2010b). A 2015 meta-analysis concluded that modafinil has genuine cognitive enhancing effects in healthy non-sleep-deprived individuals, without causing serious side effects or mood changes (Battleday and Brem, 2015). Although studies employing simple tests (assessing one or two cognitive sub-functions) did not detect many benefits of modafinil (possibly due to ceiling effects), in more complex tasks modafinil was found to exert a beneficial effect on attention, higher executive functions, and learning and memory (Battleday and Brem, 2015). In one study, modafinil improved working memory, planning, decision making and flexibility in sleep-deprived doctors (Sugden *et al.*, 2012) without showing the typical side effects of caffeine, such as tremor and anxiety (Nawrot *et al.*, 2003). Furthermore, modafinil has also been found to improve task-related motivation, which is task-specific and does not reflect a general increase in euphoria or pleasure (Müller *et al.*, 2013).

Effects of donepezil. In a systematic review regarding the use of acetylcholinesterase inhibitors by healthy people, the few existing studies, mostly about donepezil, provided no consistent evidence for a cognitive enhancing effect (Repantis *et al.*, 2010a). There was some evidence that donepezil might improve the retention of training on complex aviation tasks, verbal memory for semantically processed words and episodic memory, but the results were inconsistent, especially for episodic memory. Finally, whereas donepezil reduced memory deficits following 24 h of sleep deprivation, and only in those whose performance declined the most, there was no such effect on rested individuals. In patients with Alzheimer's disease, acetylcholinesterase inhibitors are more effective at improving attention and concentration than memory problems (Sahakian *et al.*, 1993).

Other drugs. A recent review of over 50 studies looking at other putative cognition enhancing drugs, including drugs exerting actions through other catecholaminergic mechanisms and actions on glutamate, **acetylcholine** and histamine, found mixed results (Fond *et al.*, 2015). Some studies found positive effects of **tolcapone** (inhibits dopamine degradation in the brain) and **levodopa** on memory. Further pharmacological interventions acting on **melatonin** or anti-inflammatory drugs showed positive cognitive effects, but only in single studies.

However, despite these promising findings, the effects of cognitive-enhancing drugs are quite complex. For instance, studies of methylphenidate and Adderall often demonstrate baseline-dependent effects (Allman *et al.*, 2010; del Campo *et al.*, 2013) and cognitive-enhancing drugs typically affect several neurotransmitters simultaneously, and so the optimum dose appropriate for some systems in the brain might be associated with overdosing in other systems (Sahakian and Morein-Zamir, 2015). Hence, pharmacological cognitive enhancers can have a range of effects in the same individual, enhancing specific aspects of cognition while simultaneously impairing others. It is also important to evaluate studies using cognitive-enhancing drugs to ensure that the tests are sufficiently difficult and therefore the results are not affected by ceiling effects. Another issue is related to the acute versus chronic effects of cognitive-enhancing drugs, which are likely to be different. It is not clear which pattern of use, acute or chronic, would be more beneficial for cognitive enhancement. There is evidence that several neurotransmitters might have different modes of action when released in a tonic, sustained manner compared to phasic release (Aston-Jones and Cohen, 2005; Sarter *et al.*, 2009). So far, very few studies have examined the effects of repeated doses or long-term effects. One study found that in sleep-deprived individuals, repeated doses of modafinil maintained wakefulness but did not enhance attention or executive functions (Taneja *et al.*, 2007). Although to date, studies suggest that most students use drugs for cognitive-enhancing purposes infrequently (Teter *et al.*, 2006; Maier *et al.*, 2013), patterns of use could change when students graduate and enter the world of work. Finally, it is not clear whether the effects measured in an experimental laboratory setting can be translated into everyday performance and functioning, although a number of studies did find improved performances in more complex paradigms, which might be more ecologically valid (Müller *et al.*, 2013; Battleday and Brem, 2015).

Safety, regulatory and ethical issues

The use of smart drugs by healthy individuals raises concerns about their safety as the risk of adverse side effects might outweigh the beneficial effects. Particular concerns include use in children and adolescents whose brains are still in development, as well as the abuse liability of stimulant drugs such as amphetamine and methylphenidate. In contrast, studies so far indicate that modafinil has no demonstrable abuse potential and relatively few side effects (Porsdam Mann and Sahakian, 2015). Given the increasing use of such drugs, we urgently need long-term studies on their safety and efficacy in healthy people. Another concern is that the non-medical use of cognitive-enhancing drugs by healthy people currently falls outside the scope of regulation. From a legal perspective, amphetamine and methylphenidate are classified as Schedule 2 controlled drugs, and therefore not legally obtainable without a medical prescription. Non-medical users acquire it from those who have a valid prescription, the Internet, and there have been suggestions that people may exaggerate ADHD symptoms to gain prescriptions (Talbot, 2009; Smith and Farah, 2011). A survey published in Nature reported that a third of the drugs that were used for non-medical purposes were purchased over the Internet (Maher, 2008) and users who microdose psychedelics report buying them from the dark web. This is alarming because their manufacture and supply may not be subjected to the same regulatory controls and some of the smart drugs advertised over the Internet have not been tested in humans. For instance, in the UK's biggest-ever single seizure of smart drugs, the Medicines and Healthcare products Regulatory Agency found that one of the drugs seized, Sunifiram, has not been subjected to clinical trials involving humans (Sahakian, 2014). Moreover, purchasing drugs from the Internet without consulting a medical doctor means that some people may be putting their health at risk if the drug is counter-indicated for them, for example due to high blood pressure or other medications they may be taking, which may result in drug–drug interactions.

The use of smart drugs by healthy people also raises ethical concerns, including fairness, increased academic pressure and fears of coercion, which should not be ignored. The 2015 report by the British Medical Association concluded that the magnitude of the effect of these drugs in healthy people is moderate (Nicholson *et al.*, 2015), and a 2008 report by the Academy of Medical Sciences suggests that even a 10% improvement in memory score could lead to an improvement in an A-level grade or degree class (Academy of Medical Sciences, 2008). Thus, in response to concerned students, Duke University prohibited the use of prescription drugs by students without an authorized prescription and amended its academic conduct policy in 2011 to state that 'the unauthorised use of prescription medication to enhance academic performance' was a form of cheating. As a society we should consider the reasons as to why healthy people choose to use drugs in the first place. A reliance on enhancement technologies to cope with demanding working conditions may ultimately reduce the health and wellbeing of individuals and so care must be taken to ensure that enhancement is not seen as a substitute for a healthy working environment. For instance, physical exercise, education, social interaction, mindfulness and sleep can also improve cognitive performance or overall wellbeing.

Nonetheless, in the future, the use of cognitive-enhancing drugs could prove valuable in a range of occupations, particularly in reducing fatigue-related and work-related accidents. For instance, randomized controlled trials indicate that modafinil and armodafinil increase alertness and reduce sleepiness to some extent in employees who suffer from shift work sleep disorder, although, the drugs were associated with headache and nausea (Liira *et al.*, 2015). Modafinil also showed beneficial effects in sleep-deprived doctors (Sugden *et al.*, 2012), without the counterproductive hand tremor and anxiety often associated with conventionally employed stimulants such as caffeine (Nawrot *et al.*, 2003), and in surgeons, off-label use of modafinil as a cognitive enhancer is already thought to be extensive (Franke *et al.*, 2013). There is also significant military interest in cognition enhancers for reducing errors in sleep-deprived soldiers (Caldwell *et al.*, 2004). Moreover, modafinil appears to be well-tolerated, with a low rate of adverse events and a low liability to abuse (Makris *et al.*, 2007). For these latter reasons, modafinil is likely to be preferred and is therefore a candidate for future long-term studies should the regulatory bodies (*e.g.* FDA, EMA) decide to evaluate the safety and efficacy of a cognitive-enhancing drug for use by healthy people.

It would therefore be extremely beneficial for the government and pharmaceutical industry to work together in a public–private partnership to establish the long-term safety and efficacy of currently well-used smart drugs, such as modafinil, in healthy people. If certain forms of pharmacological cognitive enhancement can be shown to be beneficial and safe in healthy individuals in the long-term, then these should be considered for use in society (Academy of Medical Sciences, 2008).

Combining cognitive-enhancing drugs and behavioural approaches to improve cognition

Whilst pharmacological drugs can be used to enhance cognition in healthy individuals and patients with neuropsychiatric disorders, non-pharmacological strategies are also beneficial (Sahakian *et al.*, 2015; Savulich *et al.*, 2017). Well-established methods to enhance cognition include education and physical exercise (Royal Society, 2011; Academy of Medical Sciences, 2012; Erickson *et al.*, 2015), and there is growing recognition of the importance of a range of lifestyle factors such as diet, sleep and social interaction (Beddington *et al.*, 2008; Rossor and Knapp, 2015). There is evidence suggesting that interventions such as learning, exercise and cognitive training activate neural networks in the brain. In rats, both learning and physical activity have been shown to increase neurogenesis in the brain (Gould *et al.*, 1999; Olson *et al.*, 2006). Both learning and exercise can have a direct effect on mental health and wellbeing across all age groups and should continue throughout life. For example, exercise improves mathematical and reading achievement in children aged 9–10 years, and also improves cognition and increases life expectancy in healthy older adults (Sallis *et al.*, 1999; Colcombe and Kramer, 2003).

Cognitive training is designed to stimulate learning and adaptive neuroplastic changes, leading to improved functioning of neural networks (Keshavan *et al.*, 2014; Sahakian *et al.*, 2017). In healthy humans, 14 h of cognitive training of working memory over 5 weeks was associated with increased activation in the working memory neural network, as well as changes in dopamine **D_1 receptor** density in the brain (Klingberg, 2010). The use of gaming technology to supply cognitive training represents a novel and innovative way for individuals to maintain good brain health and motivation and has recently been shown to improve episodic memory and functional outcome, as well as task-related motivation, in patients with schizophrenia (Sahakian *et al.*, 2015; 2017). 'Gamified' cognitive training may have the potential for use in other groups, such as healthy elderly individuals or patients with memory-related difficulties (e.g. mild cognitive impairment and traumatic brain injury). The widespread use of gaming technology could also help to reduce some of the stigma associated with mental health treatments. Combining novel techniques, such as 'gamified' cognitive training, with cognitive-enhancing drugs, may promote maximum plasticity for learning through additive or synergistic effects and also by increasing the levels of task-related motivation. In addition, the combination of cognitive-enhancing strategies could possibly improve treatment compliance of patients, for example, through beneficial effects of improvements in attending to and remembering to take medication and a feeling that their efforts can be successful (e.g. self-efficacy). However, studies that combine pharmacological and non-pharmacological methods using outcome measures of brain and behavioural changes are needed to test these hypotheses.

Novel psychoactive substances

Classes of drugs and prevalence

There are hundreds of NPS, but many of the ones used fall into one of the following categories: stimulant-type drugs (e.g. synthetic cathinones, piperazines and phenethylamines), hallucinogens (e.g. tryptamines), cannabis-like compounds, dissociative drugs (*e.g.* arylcyclohexylamines and nitrous oxide), sedatives/hypnotics and opioids (Schifano *et al.*, 2015; UNODC, World Drug Report, 2016). Based on pharmacological analysis and seizure data, the majority of NPS are synthetic cannabinoid receptor agonists, stimulants and hallucinogens (UNODC, World Drug Report, 2016). In Europe, synthetic cannabinoids and synthetic cathinones are the largest group of NPS that are monitored and in 2014 accounted for almost 70% of the total number of seizures (EMCDDA, New psychoactive substances in Europe, 2015a). Synthetic cannabinoids, also known as 'spice', are intended as replacements to cannabis and are potent agonists at the **CB_1** and **CB_2** cannabinoid receptors (Fattore and Fratta, 2011). Synthetic cathinones are the second largest group of monitored NPS (EMCDDA, New psychoactive substances in Europe, 2015a) and are stimulants that mimic the effects of MDMA, amphetamine and cocaine. These drugs usually promote the release of the monoamines 5-HT, dopamine and noradrenaline or inhibit their re-uptake (Schifano *et al.*, 2015). Mephedrone tends to be the most popular drug in the synthetic cathinone category and has become an established drug in the drug market since its first appearance in 2008/2009 (Home Office, New Psychoactive Substances in England, 2014). The recreational use of inhaled nitrous oxide has become increasingly popular, particularly in the UK and the US (Kaar *et al.*, 2016). Preliminary findings from the 2016 Global Drug Survey indicate an increase in the use of nitrous oxide or 'laughing gas' in the UK and globally, rendering it the seventh most popular drug in the world (Global Drug Survey, 2016). Nitrous oxide acts as a partial **μ**, **κ** and **δ** opioid receptor agonist (Gillman and Lichtigfeld, 1998) and is also a glutamate **NMDA** receptor antagonist, leading to a decrease in excitatory neurotransmission throughout the CNS *via* non-competitive glutamate inhibition (Jevtović-Todorović *et al.*, 1998).

The majority of NPS users appear to be young males (aged 15–24 years) from urban areas, although not exclusively (Crime survey for England and Wales, 2015; Palamar *et al.*, 2015; Global Drug Survey, 2016; Soussan and Kjellgren, 2016). In the UK, 2.6% of young people (aged 16–24 years) reported using NPS last year (Crime survey for England and Wales, 2015). Moreover, there are indications of an increase in NPS use among younger users. Thus, in Europe, between 2011 and 2014, lifetime use of NPS in people aged 15–24 years increased from 5 to 8% (Eurobarometer, 2014). Similarly, in the US, the prevalence of lifetime use amongst those aged 12–34 years increased from 2009 to 2013 and was at 1.2% in 2013 (Palamar *et al.*, 2015). This is concerning, given the relative lack of information on their acute and long-term effects on physical and mental health.

The Internet is a common way of acquiring NPS, with some surveys reporting that 58 (Global Drug Survey, 2016) and 60.4% (Soussan and Kjellgren, 2016) of respondents bought NPS online. Thus it is possible that vulnerable groups such as adolescents may be exposed to drug websites that provide direct drug purchase opportunities (Vardakou *et al.*, 2011). However, the Crime Survey for England and Wales found that the most popular sources of NPS were from a shop, friend or known dealer (Crime Survey for England and Wales, 2016). These discrepancies could reflect the legality of NPS; for instance, before the introduction of legislation, users generally obtained mephedrone *via* the Internet, whereas after the ban went into effect, they started buying from dealers (Winstock *et al.*, 2010; McElrath and O'Neill, 2011).

Characteristics and motivations of users

Surveys so far suggest that some of the primary motivations for NPS use include curiosity (Mazurkiewicz *et al.*, 2013) and pleasure and enjoyment (Soussan and Kjellgren, 2016), which are likely to be similar to motivations for taking traditional illicit drugs. However, it appears that for specific groups of people there are distinct attractions to using NPS as opposed to controlled drugs. Evidence so far indicates that the motivations for use of NPS vary greatly depending on the user group and drug type and may also include factors such as legal status, availability and cost, as well as the desire to avoid detection.

The so-called 'psychonauts', 'cyber-psychonauts' or 'e-psychonauts' are typically educated and informed NPS users who report high levels of pharmacological and IT knowledge and appear to be mainly young, unmarried males (Orsolini *et al.*, 2015). Cyber-psychonauts report using NPS for philosophical 'inner exploration' but also to intentionally experiment with novel mind-altering substances. They enjoy searching for information about chemicals online and document and share their drug experiences with like-minded individuals within online drug communities, including on social media (Orsolini *et al.*, 2015). Online NPS communities thus represent a vital tool through which cyber-psychonauts hope to acquire and share NPS-related knowledge. As such, one study found that cyber-psychonauts typically preferred buying NPS online because they valued the information provided by NPS users on forums, including information on purity, safe dosage and potential health risks (O'Brien *et al.*, 2015). In this group of users, purity and ease of access/ availability were identified as the most important criteria when it came to buying NPS (O'Brien *et al.*, 2015).

Soussan and Kjellgren (2016) conducted a comprehensive survey to establish the motivations for use of various different NPS. Synthetic cannabinoids were the least appreciated drug and the least likely to be used again, which probably reflects their quite severe side effects (Palamar and Acosta, 2015). The use of synthetic cannabinoids was, to a larger extent than any other drug group, motivated by circumstances such as price, legal status, availability and non-detectability in screening tests, which further establishes their position mostly as a substitute for users in need of an alternative to traditional cannabis. Thus, the surge in the use of synthetic cannabinoids amongst prisoners is also likely to be driven by the formerly legal status of these drugs and the desire to avoid detection in drug screens (Home Office, New Psychoactive Substances Review, 2014). In the study by Soussan and Kjellgren (2016), motivations for stimulant use included enhancement of mental and physical abilities as well as facilitation of social situations. The main motivation for hallucinogens and dissociatives was self-exploration or spiritual attainment. A study investigating the use of nitrous oxide found that nitrous oxide is generally consumed by males in their 20s in clubs and at festivals (Kaar *et al.*, 2016). Opioids and GABA activating drugs were primarily used to cope with life challenges, including pain, boredom, emotions, problems, anxiety and sleep deprivation, but were also significantly associated with habit and addiction (Soussan and Kjellgren, 2016).

In some cases, there is evidence indicating that NPS function as substitutes at times of low availability and poor quality of established illicit drugs. For example, mephedrone became an attractive cocaine and MDMA replacement when these substances became less available in 2008/2009 (Global Drug Survey, 2016). It is likely that the increases now being observed in the potency and purity of established drugs may have implications for the consumption of NPS. For instance the 2016 Global Drug Survey found that whereas 4 years ago the non-availability and poor quality of other drugs was a motivating factor for NPS use, in recent years there is greater importance on perceived value for money and ease of access online (Global Drug Survey, 2016). Similarly, in a recent study focusing on the use of mephedrone and other synthetic cathinones in Slovenia, the main reasons for their rising popularity included their positive effects, lower price and perceived purity compared with classic stimulant drugs, whereas the inaccessibility of MDMA and the legal status of NPS were not so important (Sande, 2016). The results from surveys show that NPS use is predominantly confined to existing traditional illicit drug users (Home Office, New Psychoactive Substances Review, 2014; Soussan and Kjellgren, 2016), which may also explain why legality is not usually a motivator for users.

Risks of increasing NPS use

The fact that many NPS are advertised or still referred to as 'legal' may not only facilitate their popularity but also lower the perception of the risks associated with their consumption (Castaneto *et al.*, 2014). This is worrying, especially given the growing evidence that NPS use is associated with a variety of potentially harmful effects. For instance, synthetic cannabinoids contain chemicals that are more potent than **THC** found in traditional cannabis, leading to concerns about their long-term effects on health (Castaneto *et al.*, 2014). They have also been linked to high numbers of emergency department visits (Castaneto *et al.*, 2014), with one study reporting the risk of requiring emergency medical treatment to be 30 times greater following the use of synthetic cannabinoids than following traditional cannabis (Winstock *et al.*, 2015). It is, therefore, a matter of concern that amongst adolescents in the USA synthetic cannabinoids were the most popular choice of drug after cannabis in 2011 (Johnston *et al.*, 2014), although their use may now be declining (Johnston *et al.*, 2016).

Although, to date, no study has investigated cognitive deficits in synthetic cannabinoid users, a recently published study showed that long-term use (more than five times a week for at least 1 year) of synthetic cannabinoids was associated with white matter abnormalities in adolescents and young adults (Zorlu *et al.*, 2016). Disturbed brain connectivity in synthetic cannabinoid users may underlie cognitive impairment, particularly as synthetic cannabinoid intake has been associated with psychosis (Papanti *et al.*, 2013). Frequent, long-term use of traditional cannabis has been associated with addiction, cognitive impairment, cognitive decline and a possible increased risk of psychotic illness (Volkow *et al.*, 2014; Hall, 2015; Curran *et al.*, 2016), with some studies reporting that cognitive decline and cognitive impairment were largest in those who started using traditional cannabis during adolescence (Ehrenreich *et al.*, 1999; Gruber *et al.*, 2012; Meier *et al.*, 2012). Therefore, future research studies should determine whether synthetic cannabinoids are also associated with detrimental effects in the adolescent brain and whether prevention and policy efforts should target adolescents. A surge in the use of synthetic cannabinoids amongst prisoners, who use these drugs to evade detection in drug screens, has been associated with mental and physical health problems (Prisons and Probations Ombudsman for England and Wales, Learning lessons bulletin: Fatal incident investigations issue 9, 2015).

The use of synthetic cathinones has also been linked to high numbers of emergency department visits (Wood *et al.*, 2014) and users of both synthetic cannabinoids and mephedrone have described feelings of dependency (Schifano *et al.*, 2011; Spaderna *et al.*, 2013) (Global Drug Survey, 2016). Particularly alarming has been the increase in the number of people who inject NPS and engage in higher levels of risky behaviours, resulting in a higher risk of acquiring HIV and hepatitis C (Public Health England, Shooting Up, 2016). For example, one study has reported an increase in the use of mephedrone amongst gay and bisexual men who inject the drug for use in a sexual context ('chemsex'), and who may share injection equipment and engage in unprotected sex (Bourne *et al.*, 2014).

Summary and conclusion

The increasing lifestyle use of cognitive-enhancing drugs and various NPS by healthy people indicates the desire for individuals to enhance cognitive function, creativity as well as pleasure and motivation. Cognitive-enhancing drugs have been shown to moderately enhance cognitive performance in healthy individuals (Repantis *et al.*, 2010a, b; Battleday and Brem, 2015; Nicholson *et al.*, 2015; Porsdam Mann and Sahakian, 2015), and modafinil may be beneficial in certain populations, such as sleep-deprived doctors and shift workers (Sugden *et al.*, 2012; Liira *et al.*, 2015). Therefore, the advantages of well-established smart drugs, such as modafinil, in healthy people should be considered and researched further. In a knowledge economy, cognitive enhancement is attractive to many individuals for self-improvement. However, as a society we should not ignore the negative factors that may drive people to take these drugs, such as stress and increasing demands in the workplace. It will also be important to consider ethical issues of coercion and fairness, safety issues and societal values and views. Aside from drugs for cognitive enhancement, healthy individuals are turning to a wide variety of NPS for enhancing creativity, inner exploration, self-medication and for pleasure and enjoyment. NPS use has completely changed the drug scene in the last 8 years, with several NPS now firmly established in the lives of many drug users. The increased availability of these compounds from the Internet, their reduced cost and formerly legal status has helped fuel their popularity. It is, however, becoming apparent that these substances can be associated with severe adverse health events. Their long-term effects on physical and mental health remain to be determined. More research is needed into these substances and the patterns of their use to better understand their acute and long-term health effects as well as to establish effective harm reduction strategies. The increasing lifestyle use of drugs by healthy people for the purposes of enhancing cognition, creativity, motivation and pleasure is changing society as we know it.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015a,b,c).

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